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Subject: Public Comments on the HPV Challenge Program Test Plan for Tin bis(2-ethylhexanoate) (Tin EHA, CAS Number 301-10-0) by Members of the Metal Carboxylates Coalition (Arkema, Inc. and Rohm & Haas Company).

The following comments on the HPV Challenge Program test plan for tin 2-ethylhexanoate by members of the Metal Carboxylates Coalition (Arkema, Inc. and Rohm & Haas Company) are submitted on behalf of People for the Ethical Treatment of Animals, the Physicians Committee for Responsible Medicine, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These health, animal protection, and environmental organizations have a combined membership of more than ten million Americans.

In our August 15, 2006 submission, we requested that EPA reopen the comment period for the metal carboxylates test plans, since, as a result of breaking up the category, the numbers of animals to be used has greatly increased and there are a number of serious scientific and animal welfare concerns that need to be addressed. This is the seventh set of comments that we have submitted on the new individual test plans.

The sponsoring companies are proposing to conduct a 7 day repeated dose toxicity test and an acute fish toxicity test. If conducted, the acute fish toxicity test will cause the suffering and death of approximately 120 animals. Since we are unaware of any OECD guidelines for a 7 day repeated dose test, none are specified in the test plans, and no 7 day test is part of the SIDS protocols on which the HPV program is based, we are unable to estimate the number of animals such a test would consume.

This test plan violates the principles of the October 1999 agreement among the EPA, industry, and health, animal protection, and environmental organizations, as well as the December 2000 *Federal Register* notice reconfirming that agreement which directed HPV Challenge Program participants to maximize the use of existing and scientifically adequate data to minimize further testing.

Tin 2-ethylhexanoate is used primarily as a cross-linking agent in the production of flexible polyurethane foams and as a catalyst in the production of polymers. The sponsoring companies note that metal carboxylates readily dissociate into free metal and free acid. The proportion of dissociated salt is dependent on the pH, and the dissociation constant (pKa) is the pH at which 50% dissociation occurs. The pKa value for tin EHA is reported to be 5.088 as determined in studies conducted by the Metal Carboxylates Coalition. These values indicate that complete dissociation will occur at the physiologically relevant pH of the mammalian stomach (pH 1.2).

The sponsoring companies conclude therefore, that when administered orally, the toxicity of tin EHA is due to the independent action of 2-ethyl hexanoic acid (2-EHA) and the free tin ion. As a result, mammalian toxicity data for 2-EHA and the free tin ion, or its simple metal salts, can serve as surrogate data for tin EHA.

A 7 day repeated dose toxicity test is proposed for tin 2-ethylhexanoate. Although no existing data are summarized for reproductive or developmental toxicity endpoints for tin EHA, data from a lifetime carcinogenicity study are summarized. Since one sarcoma of the uterus is reported in this study[1], reproductive organs were apparently examined. Existing data is summarized for repeated dose and developmental toxicity endpoints for stannous chloride including data from an NTP carcinogenicity study in which reproductive organs were examined. Existing data is summarized for repeated dose, reproductive and developmental toxicity endpoints for 2-ethyl hexanoic acid. The theoretical discussion of metal carboxylates dissociation presented in the test plan and summarized above clearly shows, and the sponsoring companies affirm, that data for stannous chloride and 2-EHA can serve as surrogate data for tin EHA. The only justification offered for proposing this duplicative test is to "demonstrate that the toxicity of the tin EHA is not more than the toxicity of the dissociation products". In its comments on the Aluminum Stearates Category test plan, EPA specifically rejects this approach of conducting 7 day repeated dose studies on the metal carboxylate in order to confirm existing data for its dissociation products, noting that "it is not clear how the proposed 7-day repeated-dose bridging study would demonstrate that the dissociation products data are representative of aluminum stearates toxicity". The comments also stress that EPA "does not support further testing for mammalian toxicity endpoints." Further, we are unaware of any OECD guideline for a 7 day repeated dose test and none is specified in the test plan. We strongly object to the proposal of this non-standard, unspecified test and urge EPA to again reject it along with any further testing for mammalian toxicity endpoints.

Because the Metal Carboxylates Coalition submitted its original test plan in 2003, it may be unaware that a similar approach, using existing data on dissociation products, was subsequently endorsed by the EPA and all stakeholders in 2004 for E. I. du Pont de Nemours & Company's test plan for triisopropylborate, a compound which breaks down to isopropanol and boric acid in water (see http://www.epa.gov/oppt/chemrtk/triprobt/c14841tc.htm). This approach has been used in a number of other test plans as well in which compounds dissociate at low pH and the toxicity data on the dissociation products has been used to meet the SIDS requirements.

An acute fish toxicity test is also proposed for tin 2-ethylhexanoate. Existing data is summarized for ecotoxicity endpoints in fish, daphnia and algae for stannous chloride and 2-ethyl hexanoic acid. While the sponsoring companies affirm that since tin EHA dissociates at environmental pH, the data for the dissociation products can be used to represent its aquatic toxicity, they offer no justification for proposing this duplicative test. We urge EPA to reject this test which the sponsoring companies themselves argue is unnecessary. In addition, no reliable ecotoxicity data for aquatic plants or invertebrates exist for tin EHA. The fish test is intended to show whether exposure to tin EHA will result in large-scale fish death thereby predicting economic loss and ecologic damage. If this exposure kills the food on which fish subsist, it could deplete fish populations even without direct fish toxicity. Since the toxicity of tin EHA to aquatic plants and invertebrates is still unknown, a test on fish is premature. Finally, the applicability of ECOSAR

and non-animal ecotoxicity tests, such as the DarT test[2] and TETRATOX test[3] should be considered. If a fish acute toxicity test is still perceived to be required, ECVAM's Ecotoxicology Task Force recently published an evaluation of a fish acute threshold (step-down) test concept with the potential to reduce the number of fish used in ecotoxicity testing by 53.6%-71.2%.[4]

In summary, we strongly object to the proposed 7 day repeated dose toxicity test simply to demonstrate that the toxicity of tin EHA is not more than that of its dissociation products. We urge EPA to reject this proposed test along with any further testing for mammalian toxicity endpoints as it has already done in its comments on the Aluminum Stearates Category test plan. We also urge EPA to apply similar reasoning in its consideration of the proposed acute fish toxicity test and to reject it as well. At a minimum, the applicability of the suggested alternatives to this test should be considered.

Sincerely,

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Research & Investigations

[1] Roe, F.J.C., E. Boyland, and K. Millican. 1965. Effects of oral administration of two tin compounds to rats over prolonged periods. *Food. Cosmet. Toxicol.* 3(2):277-280.
[2] Nagel, R. 2002. DarT: the embryo test with the zebrafish *Danio rerio*: A general model in ecotoxicology and toxicology. *ALTEX* 19 (Suppl. 1), 38-48.
[3] Schultz, T.W. 1997. TETRATOX *Tetrahymena pyriformis* population growth impairment endpoint: A surrogate for fish lethality. *Toxicological Methods* 7, 289-309.
[4] Jerama, S., et al. 2005. A strategy to reduce the use of fish in acute ecotoxicity testing of new chemical substances notified in the European Union. *Regulatory Toxicology and Pharmacology* 42, 218–224.